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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,789	01/25/2002	Paul Haynes	NADII.022A	9365
25297	7590	12/14/2004	EXAMINER	
JENKINS & WILSON, PA 3100 TOWER BLVD SUITE 1400 DURHAM, NC 27707			RUSSEL, JEFFREY E	
			ART UNIT	PAPER NUMBER
			1654	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/057,789

Applicant(s)

HAYNES ET AL.

Examiner

Jeffrey E. Russel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 June 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4 sheets.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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1. The statement of no new matter has been received, and the Sequence Listing filed June 28, 2002 is now approved.
2. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structures of the compounds being claimed is unclear. With respect to formulas (II) and (III) and the -NH-X- groups which are present, when X is an amino acid sequence, it is not clear if the sequence is oriented in the conventional direction, with the N-terminus on the left-hand side and resulting in the formation of a -NH-NH- group, or if the sequence is oriented with the C-terminus at the left-hand side so that a more conventional -NH-C(O)- bond results. For analogous reasons, it is not clear what structure the -Z-Link group in formulas (II) and (III) has when Z is one of the amide bond formulas. With respect to formula (II) and variable Y, it is not clear if the amide bond of formula -C(O)-NR- represents a group in addition to the carbonyl group which would be present at the end of the Epitope Tag Site and in addition to the amino group which would be present at the beginning of the Protease Cleavage Site. If so, then the compound of formula (II) could comprise a -C(O)-C(O)-NR-NH- group, which is not typical of most peptide compounds. Claim 1 requires Link to be Lys- ϵ -iodoacetamide or Orn- δ -iodoacetamide. However, claim 2 does not require the presence of such groups, but rather requires the presence of -CH₂CH₂CH₂CH₂-NH-C(O)-CH₂I or -CH₂CH₂CH₂-NH-C(O)-CH₂I groups in addition to C-terminal lysine or ornithine residues. It is unclear if these groups are in addition to the sidechains of the lysine or ornithine residues, or if they represent lysine and ornithine residues with modified sidechains. Claim 10 is indefinite because

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it is unclear if the iodoacetamide groups are attached to the side chains of the glycine, alanine, aminobutyric acid, and valine residues, or if they are attached to the C-termini of these residues.

3. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The compounds of claim 2 do not appear to comprise a Lys- ϵ -iodoacetamide or an Orn- δ -iodoacetamide group as required by the independent claim. This objection is related to the rejection under 35 U.S.C. 112, second paragraph, set forth in section 2 above.

4. Claims 1-10 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/264,576 because the provisional application '576, under the test of 35 U.S.C. 112, first paragraph, does not disclose compounds in which X can be between 1 to 10 amino acids (note that the provisional application discloses between 10 to 30 amino acids), does not disclose Z being glycine, alanine, a synthetic amino acid, or γ -aminobutyric acid, does not disclose compounds having the structures recited in instant claim 2, and does not disclose compounds of formula (III).

Claims 2 and 10 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/305,232 because the provisional application '232, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed subject matter.

Claims 1 and 3-9 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/305,232 because the provisional application '232, under the test of 35 U.S.C. 112, first paragraph, does not disclose compounds in which X can be

between 1 to 10 amino acids (note that the provisional application discloses between 10 to 30 amino acids), and does not disclose Z being glycine, alanine, a synthetic amino acid, or γ -aminobutyric acid.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1 and 3-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Washburn et al (U.S. Patent Application Publication 2003/0068825). Washburn et al teach compounds having the same structures recited in Applicants' claims. See, e.g., paragraphs [0256] through [0275]. The amino acids which are present in compounds [0256] to [0270] all correspond to Applicants' formula (II) in which, e.g., the Protease Cleavage Site is ENLYFQG, Y is an amino acid sequence of 10, 9, or 8 amino acids, A=0, and X is an amino acid sequence of 1, 2, or 3 amino acids. Compounds [0272] through [0275], which are identical to those recited in instant claim 2, necessarily have a group X which is an amino acid sequence comprising 0 to 3 amino acids.

The disclosure of Washburn et al relied upon in the above rejection is entitled under 35 U.S.C. 119(e) to the benefit of the filing date of Washburn et al's provisional application 60/305,169. See, e.g., page 62, lines 9-29, of the provisional application '169. Accordingly, Washburn et al has an earlier effective filing date than instant claims 1 and 3-9 (see section 9 above) and is available as prior art against these claims under 35 U.S.C. 102(e).

Washburn et al does not have an earlier effective filing date than instant claims 2 and 10 (see section 9 above), and accordingly is not prior art against these two claims.

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7. Applicant's arguments filed November 4, 2004 have been fully considered but they are not persuasive.

The rejection of the claims under 35 U.S.C. 112, second paragraph, is maintained. Applicants argue the "NH" in the "NH-X" group in the two formulas is intended to show the attachment point of the Acyl, i.e. that the "NH" represents the N-terminus of the amino acid sequence X and does not represent a group in addition to the amino acid sequence. However, this interpretation offered by Applicants immediately raises the question of what does the "NH" represent when X is an amino acid sequence comprising 0 amino acids - does "NH" represent the N-terminus of the Epitope Tag Site? When X is an amino acid sequence comprising 0 amino acids and A=0, or when X is -C(O)-NR- or when is -C(O)-, what does NH represent - does the "NH" disappear from the formula because there is no amino terminus to represent, or for these situations does NH represent an actual amino group which is physically present in the compounds in addition to all of the other groups? Applicants point to specific compounds in paragraphs [0067]-[0068] as supporting Applicants' interpretation of the chemical formulas. However, these specific compounds merely repeat the terminology and do not explain what was intended by Applicants. For example, in the compounds of these paragraphs, the "NH" could represent the amino terminus of the following amino acid sequences, or the "NH" could represent an amino group in addition to whatever groups are present in the following amino acid sequences.

Continuing on with Applicants' interpretation of the "NH" group in the two formulas, if this group merely represents the N-terminus of the amino acid sequence X, then when X is -C(O)-NR-, does the "NR" merely represent the N-terminus of the Epitope Tag Site, or is this

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NH group in addition to those present in the Epitope Tag Site? If the former interpretation is intended, then it is not known what difference there is between the claim recitations that X can be -C(O)-NR- and that X can be -C(O)-. If the latter interpretation is intended, then the resulting compound would comprise a -C(O)-NR-NH- group, which is not typical of most peptide compounds.

On pages 9 and 10 of the remarks, Applicants refer to a 5'-3' direction, to a "3' amino acid", to a "5' amino group", to a "conventional 5' to 3' orientation", etc. However, amino acids and amino acid sequences do not have 5' or 3' positions and do not have 5'-3' orientations. This is terminology used exclusively with oligonucleotide sequences, and has no relevance to amino acid sequences.

Applicants argue that Y represents the connection of the carboxy terminus of the Epitope Tag Site with the amino terminus of the Protease Cleavage Site. However, this interpretation does not hold when A=0 and when X is either -C(O)-NR- or is an amino acid sequence comprising 0 amino acids. With respect to the interpretation of the group Z in the two formulas, Applicants argue that the amide bonds show that an amino acid sequence linked to Z, or forming part of Z, can be present in either orientation, i.e. the conventional N-terminus to C-terminus, or the opposite orientation C-terminus to N-terminus. However, only in formula (II) can an amino acid sequence be linked to Z, that amino acid sequence being the Protease Cleavage Site. Also, because at page 10, lines 3-4, of the remarks, Applicants have argued that the Protease Cleavage Site is in the conventional N-terminus to C-terminus orientation, it is contradictory to argue at page 10, lines 8-11, that Z can be linked to N-terminus of this amino acid sequence.

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Applicants have yet to provide a consistent interpretation of the formulas recited in the claims, and, as indicated in the first Office action and Applicants' response thereto, the examiner has not been able to guess what interpretation was intended by Applicants. One skilled in the art would be unable to determine whether a particular group in the claimed formulas and compounds represents a group which is actually present in and of itself in the claimed compounds, or whether the particular group merely represents the orientation of other groups present in the claimed compounds. The claims remain indefinite in the absence of clarifying claim language which permits one skilled in the art to understand what Applicants are claiming.

With respect to the lack of correspondence between the formulas of independent claim 1 and the compounds of dependent claim 2, the examiner maintains his position. This rejection could be overcome by amending claim 2 so that it uses the same terminology used in the independent claim, i.e. so that it uses "Lys- ϵ -iodoacetamide" instead of "K-CH₂CH₂CH₂CH₂-NH-C(O)-CH₂I" and so that it uses "Orn- δ -iodoacetamide" instead of Orn-CH₂CH₂CH₂-NH-C(O)-CH₂I.

With respect to section 9 of the first Office action, it can not be assumed that the -NH- which occurs after "Acyl" in the compounds of claim 2 represents the amino terminus of the following amino acid sequence. This is because the interpretation of -NH- in the formulas of claim 1 is unclear. As noted above, it is possible that -NH- in the formulas represents the amino terminus of an attached amino acid sequence, and it is possible that -NH- represents a group which is actually present in and of itself in the claimed compounds.

The rejection over Washburn et al (U.S. Patent Application Publication 2003/0068825) is maintained. That the general formula of Washburn et al does not anticipate or suggest

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Applicants' claims does not mean that the specific compounds of Washburn et al can not anticipate Applicants' claims.

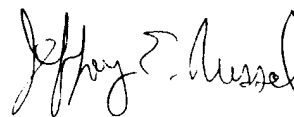
8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
December 10, 2004